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Long-Term Outcome in Women Less Than 30 Years of Age With Breast Cancer

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Background and Objectives: Young age at diagnosis is associated with poor prognosis in female breast cancer, but few studies report long-term outcome in women less than 30 years of age. We evaluated 30-year survival in this patient population.
Methods: A retrospective analysis was performed of 29 women less than 30 years of age who were diagnosed with breast cancer between the years 1953 and 1983. All but two patients were followed either until death or for a minimum of 30 years.
Results: Actuarial 30-year survival was 19% for the entire group and 10% for women with invasive ductal carcinoma. Twenty-two (92%) of 24 deaths were due to metastatic breast cancer, including three deaths occurring after disease-free intervals of more than 12 years.
Conclusions: Breast cancer in our study population of women less than 30 years of age was a highly lethal disease, particularly in patients with invasive ductal carcinoma. The phenomenon of late death after a long disease-free interval is important in the interpretation of data reflecting newer forms of breast cancer treatment.
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KEY WORDS: **breast neoplasms; young age; prognosis; survival**

INTRODUCTION

In 1940, Dr. James Ewing stated, ''The relatively malignant course of most structural types of [breast cancer] in young subjects is widely recognized'' [1]. The association between young patient age and poor outcome in breast cancer has been attributed to both later stage at presentation and a more aggressive form of the disease [2]. In recent years, however, the role of age in determining the aggressiveness of breast cancer has become somewhat controversial [3–5]. It has been suggested that with the use of modern adjuvant chemotherapeutic regimens, survival in younger women has approached that in older women [6]. In addition, other studies have used multivariate analysis to identify the influence of various factors on breast cancer outcome, and have found young age not to be an independent predictor of poor outcome [7,8].

An early clinical series found that death from breast cancer was most frequent in the 21- to 50-year age group, when compared to women in the 51- to 70-year and in the 71- to 100-year age groups [9]. Subsequently, women within the less than age 50 or premenopausal groups were compared, and again younger women were reported to have poorer outcomes [10]. There has now been significant study of large groups of women less than age 35–40. There are, however, relatively few studies of women diagnosed before age 30. In addition, most of the data on outcome of breast cancer reflect 5- to 10-year follow-up, and it has been suggested that patterns of survival may change when patients are followed for longer periods [11,12]. Few data exist, however, regarding outcomes of this disease 20 years or more after diagnosis.

Breast cancer in young women has a profound effect on the length and quality of life. Although young women comprise the majority of patients seen in breast clinics [13], diagnosing breast cancer in this population may be more difficult than it is in older women [14]. Because of the frequent absence of comorbid disease, young women

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TABLE I. Demographics, Tumor Characteristics, Treatment, and Outcome of 29 Women Diagnosed With Breast Cancer Before Age 30*

Case No.	Age at diagnosis	Pregnant at diagnosis	Histologic type	Stage	Surgical treatment	Status at last follow-up[a]	Survival[b] (yr)	DFI[c] (yr)
1	26	No	Ductal	II	RM	DOD	3.1	1.0
2	28	Yes	Ductal	—[d]	RM	DOD	1.8	1.7
3	28	No	Ductal	II	RM	NED	(19.0)	—
4	27	No	Ductal	II	RM	DOD	8.4	3.7
5	28	Yes	Ductal	I	MRM	DOD	6.8	3.2
6	28	No	Ductal	III	RM	NED	(31.8)	—
7	29	No	Ductal	II	RM	DOD	2.3	1.8
8	24	No	Ductal	II	RM	DOD	7.5	3.7
9	27	No	Medullary	II	RM	NED	(32.5)	—
10	26	Yes	Ductal	III	MRM	DOD	4.6	1.8
11	28	No	Ductal	III	MRM	DOD	1.2	0.7
12	27	Yes	Ductal	III	RM	DOD	13.0	12.7
13	28	No	Scirrhous	II	RM	DOD	4.3	1.2
14	27	No	Ductal	—[d]	MRM	DFD	14.9	—
15	29	No	Scirrhous	II	RM	DOD	25.3	19.9
16	28	No	Ductal	II	RM	DOD	3.5	2.3
17	29	Yes	Comedo[c]	III	MRM	NED	(20.1)	—
18	26	No	Ductal	IV	PM	DOD	0.4	0
19	28	No	Ductal	II	RM	DOD	0.8	0.7
20	28	No	Ductal	II	MRM	DOD	17.3	14.6
21	27	No	Ductal	III	MRM	DOD	3.8	2.3
22	28	No	Ductal	III	none[e]	DOD	1.4	0.4
23	29	No	Medullary	II	RM	NED	(30.7)	—
24	28	No	Ductal	III	MRM	DOD	2.5	2.0
25	28	No	Ductal	III	MRM	DOD	3.3	2.8
26	26	No	Scirrhous	II	RM	DOD	2.3	0.5
27	29	No	Colloid	II	RM	DFD	31.8	—
28	27	Yes	Lobular	III	RM	DOD	2.7	0.3
29	20	Yes	Ductal	II	SM[f]	DOD	1.9	1.0

*RM, radical mastectomy; MRM, modified radical mastectomy; PM, partial mastectomy (palliative); SM, simple mastectomy; DOD, died of disease; NED, no evidence of disease; DFD, died free of disease; DFI, disease-free interval from date of surgery; 0, never rendered clinically disease-free; —, no evidence of disease at last follow-up, or died free of disease.
[a]Patients 14 and 27 died of ovarian and gastric cancer, respectively.
[b]From date of diagnosis; parentheses indicate still alive at last follow-up.
[c]With focal invasion.
[d]Not staged because of insufficient data.
[e]Biopsy was performed.
[f]No documentation of why more extensive procedure was not performed.

are often optimal candidates for the more aggressive treatment regimens that are being developed. These factors, and the paucity of extended follow-up data in women less than age 30, prompted us to study long-term outcome in a group of women diagnosed with breast cancer at a very early age.

MATERIALS AND METHODS

Patient data were obtained from the tumor registry of a large, urban teaching hospital. Inclusion criteria for the study included female sex, diagnosis of invasive breast cancer made during 1953–1983, and age less than 30 years at diagnosis. Data collected included age at diagnosis, pregnancy status, surgical pathology, stage of disease, treatment, disease-free interval, and survival. Data regarding patient race were unavailable for most cases. Patients were restaged when appropriate to conform to current TNM staging guidelines [15].

Statistical analysis was done using the Statistica 5.0 software package (StatSoft, Tulsa, OK) on a personal computer. Actuarial survival from date of diagnosis was determined by calculating Kaplan-Meier survival curves. Comparison between survival curves was performed using the log-rank test. P values of < 0.05 were considered significant. Disease-free interval was defined as the interval between surgical treatment and recurrence.

RESULTS

Demographics

Twenty-nine patients met the criteria for inclusion in the study (Table I). Mean age at diagnosis was 27 years (range 20–29 years). Seven patients (24%) were pregnant at diagnosis.

TABLE II. Distribution by Stage of 27 Women Diagnosed With Breast Cancer Before Age 30*

Stage	No. of patients (%)
I	1 (3.7)
II	15 (55.6)
III	10 (37.0)
IV	1 (3.7)

*Two patients not staged due to insufficient data.

Tumor Characteristics

Invasive ductal carcinoma was the histopathologic diagnosis in 21 (72%) of 29 tumors. Staging of 2 (7%) of the 29 patients using current TNM staging guidelines was not possible with the information available. Distribution by stage in the remaining 27 patients is shown in Table II. Notably, only one patient presented with stage I disease.

Treatment

Initial surgical management was radical or modified radical mastectomy in 26 patients. In the remaining three patients, one had biopsy of what was considered at surgery to be unresectable primary disease, one had simple mastectomy without documentation of why a more radical procedure was not undertaken, and the final patient had partial mastectomy for palliative local control after initial presentation with liver metastases.

Outcome

Five patients were alive with no evidence of disease at last follow-up, which ranged from 19.0 to 32.5 years from date of diagnosis. Of the 24 patients who died, 22 (92%) died of metastatic breast cancer. No patient was reported to have a new primary cancer in the contralateral breast. The remaining two patients died of ovarian and gastric cancer, respectively.

Rates of 5-, 10-, and 15-year survival were 45%, 34%, and 28%, respectively. Because the shortest period of follow-up was 19 years, data for these survival rates were available for all patients. The Kaplan-Meier curve used to project survival rates for longer periods is shown in Figure 1. Twenty-eight (97%) of 29 patients were followed either until death or for a minimum of 20 years, with a projected 20-year survival of 24%. Twenty-seven (93%) of 29 patients were followed either until death or for a minimum of 30 years, with a projected 30-year survival of 19%. A sharp decline in cumulative survival is seen over the first 5 years after diagnosis, after which the curve follows a less steep, but persistently downward, slope.

No significant difference in survival was observed when patients were grouped by date of diagnosis (before or after January 1, 1969, $P = 0.15$) or surgical treatment

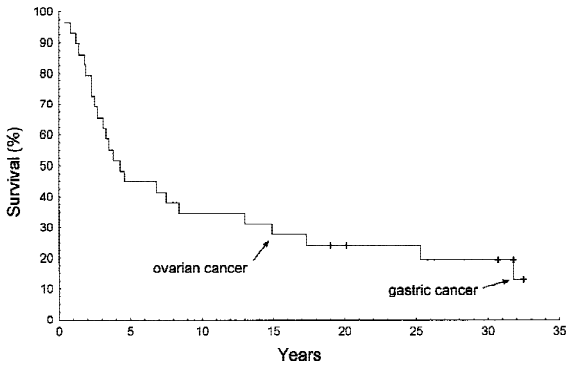

Fig. 1. Survival of 29 women diagnosed with breast cancer before age 30 (Kaplan-Meier method). Arrows, deaths not due to metastatic breast cancer.

(radical versus modified radical mastectomy, $P = 0.44$, survival curves not shown). Because stage I and stage IV disease were represented by only one patient each, survival by stage was evaluated only for women with stage II or stage III breast cancer (Fig. 2). There was no significant difference between the two survival curves ($P = 0.60$). Projected 30-year survival for patients diagnosed with invasive ductal carcinoma and those with other histologic diagnoses was 10% and 47%, respectively (Fig. 3). The difference between the survival curves was statistically significant ($P = 0.03$).

One (14%) of seven patients presenting with breast cancer in pregnancy is alive to date (no evidence of disease at 20.1 years from diagnosis). The remaining six patients died of recurrent metastatic breast cancer. There was no significant difference in the survival curves for pregnant and nonpregnant women ($P = 0.61$)(Fig. 4).

Five patients in the series had late deaths, which were defined as death occurring more than 10 years after the date of diagnosis. Of these, one each died of ovarian cancer and gastric cancer. The remaining three died of metastatic breast cancer at 13.0, 17.3, and 25.3 years after their initial diagnoses. Disease-free intervals for these three women were 12.7, 14.6, and 19.9 years, respectively.

DISCUSSION

Breast cancer is a relatively uncommon disease in young women. The probability of a woman developing breast cancer before age 40 is less than 1% [16]. Among women with breast cancer, less than 1% are between the ages of 20 and 29, the age range addressed in the present study [17,18]. Whereas young age in breast cancer has long been considered prognostic of poor outcome, several recent studies have used multivariate analysis to suggest that young age is not an independent prognostic factor and should not be used alone to determine optimal treatment [7,8]. Although this remains controversial, it is

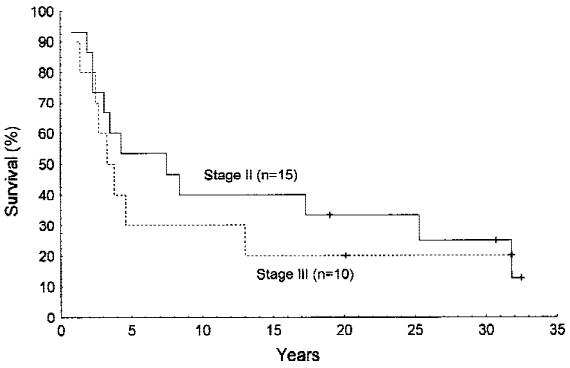

Fig. 2. Survival curves of women with stage II versus stage III breast cancer (Kaplan-Meier method, log-rank test). The difference between the curves was not statistically significant ($P = 0.60$). Stage I and stage IV disease were represented by only one patient each. Staging data were not available for two patients.

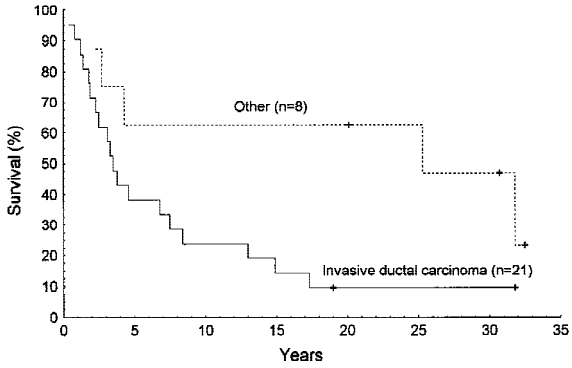

Fig. 3. Survival curves of women diagnosed with invasive ductal carcinoma versus other histologic types of breast cancer (Kaplan-Meier method, log-rank test). Survival was significantly poorer in patients with invasive ductal carcinoma ($P = 0.03$).

clear that there is a close association between young age and poor outcome.

Younger women tend to present at a more advanced stage of their disease. An analysis of the National Cancer Database found that whereas almost 50% of women over the age of 50 presented with T1 lesions, less than 30% of women aged 30 or less had T1 lesions [18]. In part, this delay in diagnosis may be due to decreased suspicion on the part of both patient and physician because of the relatively uncommon nature of breast cancer in this age group. The cyclic nodularity of the younger woman's breast may make identification of a tumor on breast examination more difficult for the woman and her doctor. In addition, the less frequent use of mammograms in young women, as well as the increased difficulty in interpreting these because of greater breast density, most likely contribute to the more advanced stage of breast cancer seen in younger women [19].

On the basis of work by Lynch and others, a subset of familial breast cancer known as hereditary breast cancer has been delineated [20]. Hereditary breast cancer is inherited as an autosomal dominant condition with high penetrance, which confers a greatly increased risk of developing breast cancer, and is estimated to affect 36–85% of patients diagnosed with breast cancer before age 30 [19]. Further research on the mutations that are responsible for hereditary breast cancer, particularly mutations in the p53, BRCA1, and BRCA2 genes, is likely to enhance our ability to provide accurate risk assessment and may have an impact on treatment recommendations.

In addition to the delay in diagnosis seen in young women with breast cancer, there is accumulating evidence to suggest that they have more aggressive tumors than those seen in older women. A recent review of breast cancer in young women cites evidence for numerous pathologic features associated with both young age and poor prognosis, including higher grade, higher S-phase fraction, greater incidence of lymph node involvement, presence of an extensive intraductal component, estrogen and/or progesterone negativity, and lymphatic or vascular invasion [19].

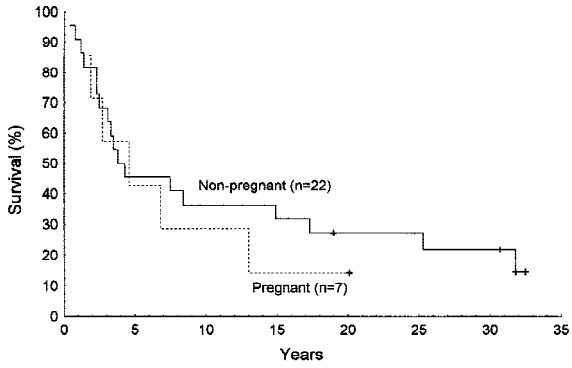

Fig. 4. Survival curves of pregnant versus nonpregnant women with breast cancer (Kaplan-Meier method, log-rank test). The difference between the curves was not statistically significant ($P = 0.61$).

In the present study, overall prognosis for women less than 30 years of age who presented between 1953 and 1983 was quite poor. Most deaths occurred within 5 years of presentation, but deaths continued from metastatic breast cancer as late as 25 years from diagnosis. Two of our patients died from diseases other than breast cancer, specifically ovarian and gastric cancer. While these patients died free of breast cancer, it is possible that some underlying genetic abnormality was responsible for both malignancies in these two patients. Perhaps as we better understand the various cancer syndromes, we will consider these the true ''disease,'' of which breast cancer may be one manifestation.

The long follow-up period we desired in our study led us to choose a study population that excluded women who presented within the last 14 years. We do not know what the 20- or 30-year survival will be like for women diagnosed with breast cancer during the current decade,

but it is clear that changes in the diagnosis and treatment of breast cancer have taken place since our study period.

First, breast cancer is now being diagnosed at an earlier stage across all age groups. While only one (4%) of 27 restaged patients in our series had a T1 lesion, National Cancer Database findings suggest that currently this figure approaches 30% [18]. Data from our hospital and the geographic area it serves may not be representative of national trends. It is clear, however, that breast cancer is being detected earlier than in the past, most likely as a result of increased patient and physician awareness, better understanding of risk factors, and, for older women, the use of routine screening mammography.

A second change over the past 15 years has been the increasing use of breast-conserving surgery. None of the women in our series had breast-conserving surgery (though during the latter portion of our study period, the feasibility of this was accepted, and its lack of use may represent local trends). Five- to 10-year survival after breast-conserving surgery, when done for appropriate indications, is equivalent to that after mastectomy [21–23]. The data suggest, however, that local recurrence rates may be higher in young women after breast-conserving surgery [24–27]. This is a concern, as we have scant data on 20- to 30-year survival after breast-conserving surgery and because this surgical option may be more frequently used in younger women.

Perhaps the most hopeful recent development in the management of breast cancer has been the use of effective adjuvant, and possibly neoadjuvant chemotherapy regimens, particularly those containing doxorubicin [28,29]. In our series, chemotherapy was used only in an attempt to control metastatic disease; no patient without known metastatic disease received planned, preoperative, or postoperative chemotherapy, and no patient received doxorubicin. Similarly, radiotherapy was used to palliate metastatic disease, particularly bone metastases. Various patients underwent oophorectomy, adrenalectomy, or hypophysectomy. There is accumulating evidence that doxorubicin-based chemotherapy improves 5- to 10-year survival in young women with breast cancer, possibly to the point of approaching the survival achieved in older women [6]. This is very promising, as most deaths from breast cancer in our series occurred during the first 5 years after diagnosis. However, we do not yet have longer-term data to predict the effect newer chemotherapy regimens will have on the phenomenon of late deaths from breast cancer. Following these women for another 10-15 years, as well as elucidation of the proper role for tamoxifen in young women [30] and more data on the efficacy of neoadjuvant chemotherapy [31], may answer some of these questions.

Finally, the use of high-dose chemotherapy with autologous bone marrow transplantation is a relatively recent development in the management of breast cancer. Early results suggest that while life may be extended somewhat by this approach, a significant improvement in long-term survival has not been achieved [32,33]. In its current form, it does not appear likely that bone marrow transplantation will have a major impact on 20- to 30-year survival.

Seven (24%) of our 29 patients were pregnant when their breast cancer was diagnosed. Previous series report that 7–14% of women of childbearing age with breast cancer are pregnant at diagnosis [34–36]. The relatively high incidence of pregnancy in our patient population may reflect the young age group we studied. While poor prognosis among pregnant women with breast cancer was initially thought to be related to the hormonal milieu during pregnancy, subsequent studies have shown that outcome for pregnant women is equivalent to that for age- and stage-matched controls [37,38]. There has been abundant documentation of significant delay in diagnosis of breast cancer during pregnancy, with a particularly concerning delay between detection of a palpable mass and definitive diagnosis [39]. Although we did not detect a significant difference in outcome between pregnant and nonpregnant women, the small sample size and overall advanced stage of disease in our study preclude any definitive conclusion regarding relative outcome in these two groups.

Although the projected 30-year survival for the women in our study was 19%, this figure dropped to 10% when only patients diagnosed with invasive ductal carcinoma were included. Invasive ductal carcinoma is the most common histologic type of breast cancer across all age groups, and the frequency of this diagnosis in our study was similar to that reported in other studies of breast cancer in young women [6,40]. Although age-dependent variation in the relative incidence of various histologic types of breast cancer in young women has been described [41], little is known about the effect of histologic type on long-term survival in this age group. Our data suggest that the diagnosis of invasive ductal carcinoma in a woman less than age 30 carries a particularly dismal long-term prognosis; this finding merits further investigation.

CONCLUSIONS

There is a relative paucity of data concerning breast cancer in women less than 30 years of age. In addition, few studies of breast cancer report outcome beyond 15 years from diagnosis. We evaluated 20- to 30-year survival in women diagnosed with breast cancer before age 30. We found that breast cancer in our patient population, particularly in women with invasive ductal carcinoma, was a highly lethal disease. While the death rate was highest in the first 5 years after diagnosis, survival continued to drop over a 30-year follow-up period, and there

were several late deaths from recurrent metastatic breast cancer after a long disease-free interval. This finding is important in the interpretation of data reflecting more recent forms of breast cancer treatment.

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